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STUDIES ON THE HEMODYNAMIC CONSEQUENCES OF PARTIAL
CARDIOPULMONARY BYPASS IN THE LAMB

FINAL REPORT

JOHN P. KINSELLA

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13. ABSTRACT (Maximum 200 words) We studied the distribution of systemic blood flow during veno-arterial extracorporeal membrane oxygenation (ECMO) in newborn lambs. We employed a three compartment model which defined partitioning of blood flow to the heart, upper body (brachiocephalic trunk), and lower body (descending aorta). The method utilized concurrent left ventricular and arterial cannular injections of radiolabeled microspheres to calculate compartment flows and solve the system of equations which defined the partition model. Seven newborn lambs (1-8 d) were studied. A baseline microsphere injection (left ventricle, LV) was performed and the animals were then placed on veno-arterial ECMO using right carotid and jugular vein cannulation. The arterial cannula was placed 2-3.5 cm above the aortic valve. After stabilization on ECMO flow rates of 50 and 100 mL/min/kg, differently labeled microspheres were injected simultaneously into the LV and arterial limb of the ECMO circuit. From the flow partition model distribution of blood flow was calculated. We found that ECMO did not change the overall distribution of blood flow to the three compartments studied. However, blood flow from the ECMO				
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circuit was preferentially directed to the upper body. Coronary arterial and abdominal organ blood flow was predominantly derived from the left ventricle at both ECMO flow rates. Coronary arterial blood flow did not significantly change on ECMO (253 ± 45 mL/min/100g at 50 mL/min/kg ECMO flow; 246 ± 50 mL/min/100g at 100 mL/min/kg ECMO flow) compared to baseline (186 ± 31 mL/min/100g). We conclude that coronary arterial blood flow is not compromised at the ECMO flow rates studied; however, the predominate source of coronary flow is from the left ventricle despite proximate placement of the arterial cannula.



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Principal Investigator's Signature 10/16/91
Date

TABLE OF CONTENTS

INTRODUCTION	1
METHODS	2
RESULTS	6
DISCUSSION	7
CONCLUSION	10
REFERENCES	17
APPENDIX	20
ADDENDUM	24

FIGURES

1. Partitioning of total systemic blood flow to heart, upper body, and lower body for control baseline, ECMO 50 mL/min/kg, and ECMO 100 mL/kg/min flow rates	11
2a. Percentage of total flow to each compartment derived from ECMO arterial cannula vs. left ventricle: upper body . .	12
2b. Percentage of total flow to each compartment derived from ECMO arterial cannula vs. left ventricle: lower body . .	13
2c. Percentage of total flow to each compartment derived from ECMO arterial cannula vs. left ventricle: heart	14
3. Coronary arterial blood flow (mL/min/100g) for control, ECMO 50 mL/min/kg, and ECMO 100 mL/min/kg flow rates . .	15

TABLE

Physiologic variables at each microsphere injection timepoint	16
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INTRODUCTION

Veno-arterial extracorporeal membrane oxygenation (ECMO) is used to provide partial heart-lung bypass support for the neonate with severe cardiopulmonary failure unresponsive to other therapies.¹ During ECMO systemic perfusion derives from both the ECMO arterial cannula and left ventricular output. Regional blood flow distribution during ECMO is not well characterized due to difficulties in studying the distribution of these two separate sources of systemic perfusion. To investigate the distribution of systemic blood flow during ECMO we employed a three compartment model which defined partitioning of blood flow to the heart, upper body (brachiocephalic trunk), and lower body (descending aorta). We studied the distribution of blood flow during ECMO in newborn lambs using a modification of the radiolabeled microsphere technique and this partitioning model.

METHODS

Animals. Seven mixed breed newborn lambs (age 1-8 d, weight 3.9-6.2 kg) were studied.

Surgical procedures. Lambs were immobilized with ketamine hydrochloride IV. Local infiltration of 1% lidocaine hydrochloride was used during instrumentation. Polyvinyl chloride catheters (0.034 in ID x 0.054 in OD; Martech Medical Products, Lansdale, PA) were placed in a femoral vein for fluid administration, and a femoral artery for blood pressure monitoring and reference sample withdrawal during microsphere injections. The left carotid artery was cannulated, without sacrificing the vessel, for reference sample withdrawal reflecting brachiocephalic trunk distribution. A catheter was advanced from a femoral artery to the left ventricle for microsphere injections. After completion of catheter placement the animals were given pancuronium (0.1 mg/kg IV), endotracheally intubated and mechanically ventilated using an infant ventilator (Bird Co., Palm Springs, CA). Ventilator settings were adjusted to obtain arterial blood gas measurements within normal physiologic ranges.

This research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to experiments involving animals. The authors adhered to the principles stated in the Guide for the Care and Use of Laboratory Animals, NIH publication 85-23, 1985.

Physiologic measurements. Distribution of blood flow was measured using the radiolabeled microsphere technique.^{2,3,4} Microspheres 15 microns in diameter labeled with ⁸⁵Sr, ¹⁵³Gd, ⁹⁵Nb, ⁴⁶Sc, and ¹¹³Sn (3M, St. Paul, MN) were used. During microsphere injections arterial reference blood samples were withdrawn into glass syringes at 2.40 mL/min by a precalibrated syringe pump (Harvard Apparatus, Dover, MA). Withdrawal began 1 min before microsphere injections and continued for 1 min following completion. The microsphere injections were not associated with changes in heart rate or blood pressure (Gould Instruments, Oxnard, CA).

Following completion of the experiments the animals were euthanatized using T-61 Euthanasia Solution (American Hoechst, Summerville, New Jersey), the position of the catheters was verified, and organs were excised for analysis of radioactivity content. The carcass was divided into upper and lower portions at the 7th thoracic vertebra, homogenized to uniform consistency, and representative samples were taken for gamma counting. Radioactivity in all samples was determined using a three-channel gamma counter (Tracor Analytic, Des Plaines, IL).

Blood samples for pH, PO₂, and PCO₂ were withdrawn anaerobically into Natelson glass pipettes and analyzed at 39.5° C using a Radiometer OSM3 blood gas analyzer (Copenhagen, Denmark). Blood hemoglobin concentration and oxyhemoglobin saturation were measured colorimetrically in duplicate using a hemoximeter (Radiometer), and oxygen content was calculated as

the product of hemoglobin concentration and oxyhemoglobin saturation.

Experimental procedures. A control microsphere injection was performed and the animals were then placed on veno-arterial ECMO using right carotid and jugular vein cannulation. The ECMO circuit and methods employed were similar to that used for ECMO in the clinical setting. A 12 or 14 Fr venous ECMO cannula and a 9.6 Fr arterial cannula (Gesco International Inc., San Antonio, TX) were placed through a paramedian neck incision. The arterial cannula was placed 2 - 3.5 cm above the aortic valve. The ECMO circuit consisted of a standard roller pump (Precision Blood Pump, Cobe Laboratories Inc., Lakewood, CO), a 0.8 M² silicone membrane oxygenator (Sci-Med, Life Systems Inc., Minneapolis, MN), a heat exchanger (Sci-Med), and a 50 ml reservoir placed within a servoregulating device limiting roller pump output to available venous blood.

After stabilization on ECMO flow rates of 50 and 100 mL/kg/min, simultaneous injections of differently labeled microspheres into the left ventricle and arterial limb of the ECMO circuit were performed. Paired arterial reference samples were withdrawn from the left carotid artery and descending aorta.

Partitioning model. A three compartment mathematical model devised by one of the authors (D.R.G.) was employed. This model was used to describe partitioning of systemic blood flow (Q) to the heart, upper body (brachiocephalic trunk), and lower body (descending aorta). The relative numbers of microspheres trapped

within each reference sample and organ of interest were used to calculate compartment flows and solve the system of equations which defined the partition model. From this model the contribution of flow from ECMO and from left ventricular output could be determined to all three compartments (heart, upper body, lower body). (see Appendix)

Statistical analysis. Differences between baseline measurements and those made at 50 and 100 mL/min/kg of ECMO flow were analyzed using analysis of variance with Fisher's least significant difference test for post hoc comparisons. Differences in blood flow derivation from LVO and ECMO at each experimental condition were analyzed using unpaired t tests with Bonferroni adjustment. The level of statistical significance was set at 0.05. Data are reported as mean \pm SEM.

RESULTS

Physiologic measurements at baseline and each ECMO flow rate are shown in the table. There were no significant differences noted for PaCO_2 , O_2 content, mean arterial pressure, or heart rate at each experimental condition. Control values for arterial pH and PaO_2 were significantly different than measurements made during ECMO at each flow rate.

We found that ECMO did not change the overall distribution of blood flow to the three compartments studied compared to control (Figure 1). Approximately 30% of total systemic flow was directed to the upper body and approximately 60% to the lower body at control and each ECMO flow rate.

However, blood flow from the ECMO circuit was preferentially directed to the upper body (Figure 2a) ($p < 0.001$). Descending aortic blood flow was predominantly derived from the left ventricle at both ECMO flow rates (Figure 2b) ($p < 0.001$), as was coronary arterial blood flow (Figure 2c) ($p < 0.001$).

Despite changes in the derivation of blood flow to organs after initiation of ECMO, there was no significant change in coronary arterial blood flow (mL/min/100g) (Figure 3) ($p = 0.49$).

DISCUSSION

The distribution of systemic blood flow during extracorporeal circulation has been of keen interest to investigators since the advent of this technique for use during cardiac surgery.⁵ Early studies focused on the distribution of blood flow during total cardiopulmonary bypass, since the technique was predominantly used for short periods intraoperatively.^{6,7,8} However, prolonged partial cardiopulmonary bypass (ECMO) has gained more widespread acceptance in recent years as an alternative therapy for neonates with life-threatening, reversible cardiopulmonary failure.¹

There are important features which distinguish ECMO from total cardiopulmonary bypass. During ECMO the venous return to the right atrium is only partially captured by the venous drainage cannula. Therefore, total systemic blood flow is the sum of residual left ventricular output and the ECMO pump flow rate. Moreover, techniques employed for organ preservation during total cardiopulmonary bypass (cardioplegia solutions, hypothermia) are not applicable during ECMO. Hence, maintenance of adequate coronary arterial blood flow during ECMO is of paramount importance.

Measurements of the distribution of systemic blood flow during ECMO are complicated by the presence of two sources of systemic arterial blood, that is, the left ventricle and the ECMO arterial cannula. In order to define the distribution of systemic blood flow in the presence of these two input sources we injected

microspheres simultaneously into each source and determined partitioning of flow using a mathematical model. The results demonstrated that, despite placement of the arterial cannula tip close to the aortic valve, there was incomplete mixing of the two sources of blood flow at the aortic root despite pump flow rates approximating 50% of the baseline (pre-ECMO) cardiac output. Thus, streaming of the two sources of blood flow occurred, resulting in preferential partitioning of the ECMO arterial cannula flow to the upper body, and LVO to the lower body and heart.

Other investigators have studied the distribution of blood flow during ECMO,^{9,10} with conflicting results. Nowlen et al⁹ used single injections of technetium-labeled microaggregated albumin to measure the relative distribution of LVO vs. ECMO arterial cannula flow compared to controls in a rabbit model. These authors reported decreased blood flow from the arterial cannula to the brain and heart in this model at 30 mL/min/kg of ECMO flow. Smith et al¹⁰ used the same method in a lamb model at 50 mL/min/kg of ECMO flow to measure the distribution of arterial cannula flow compared to the distribution of LVO in a control group. Their results showed a significantly smaller percentage of ECMO arterial cannula flow to the heart, but a significantly larger percentage delivered to the brain compared to the control group. However, in both of these studies interpretation of the results is limited by the fact that total distribution of systemic blood flow could not be assessed with the use of a

single injection of particulate indicator. In contrast, the method which we employed allowed simultaneous determination of the distribution of LVO and ECMO flow in each animal through the use of concurrent injections of microspheres and paired arterial reference sample withdrawals.

The question of proper siting of the arterial cannula to achieve adequate coronary arterial oxygenation has critical relevance to the recent application of ECMO in postoperative cardiac surgery support.¹¹ Although ECMO did not compromise coronary arterial perfusion in our model, it is apparent that oxygen delivery to the heart is more closely related to intrinsic pulmonary status (pulmonary venous saturation, LVO) than to ECMO pump arterial oxygen content. These findings are supported by the studies of Hill et al¹² and Soeter et al¹³ who found that even small amounts of left ventricular output during partial bypass precluded retrograde perfusion of the aortic arch using femoral arterial cannulation. Moreover, Secker-Walker et al¹⁴, using ECMO arterial return to the ascending aorta in adult sheep, found that an 85% bypass flow was required for a 25% increment in oxygenated blood to the coronary arteries. Similarly, Gerstmann et al¹⁵ reported that coronary arterial flow predominately derived from LVO in a baboon model of ECMO.

It is possible that, in the clinical setting, echocardiographic demonstration of turbulence created by the arterial cannula at the aortic valve would be evidence for adequate retrograde flow of well oxygenated pump blood to the

coronary arteries. However, it should be recognized that if sufficient retrograde flow from the arterial cannula is achieved by very close placement of the cannula tip to the aortic valve or very high bypass flows, then competence of the aortic valve may be compromised resulting in aortic insufficiency or frank injury. Thus, recommendations for optimal placement of the arterial cannula during ECMO await further study.

CONCLUSION

In this model, although ECMO did not change the overall distribution of blood flow, mixing of the two sources of blood flow (ECMO, LVO) was not complete. This resulted in preferential streaming of ECMO flow to the upper body and left ventricular output to the lower body. Coronary arterial blood flow was not compromised at the ECMO flow rates studied, however, the source of coronary arterial blood flow was predominantly left ventricular despite proximate placement of the arterial cannula. As such, the delivery of well oxygenated blood to the heart may be suboptimal under certain conditions during ECMO, which could have important clinical implications when this therapy is instituted for the postoperative management of compromised cardiac performance.¹¹

PARTITIONING OF SYSTEMIC BLOOD FLOW

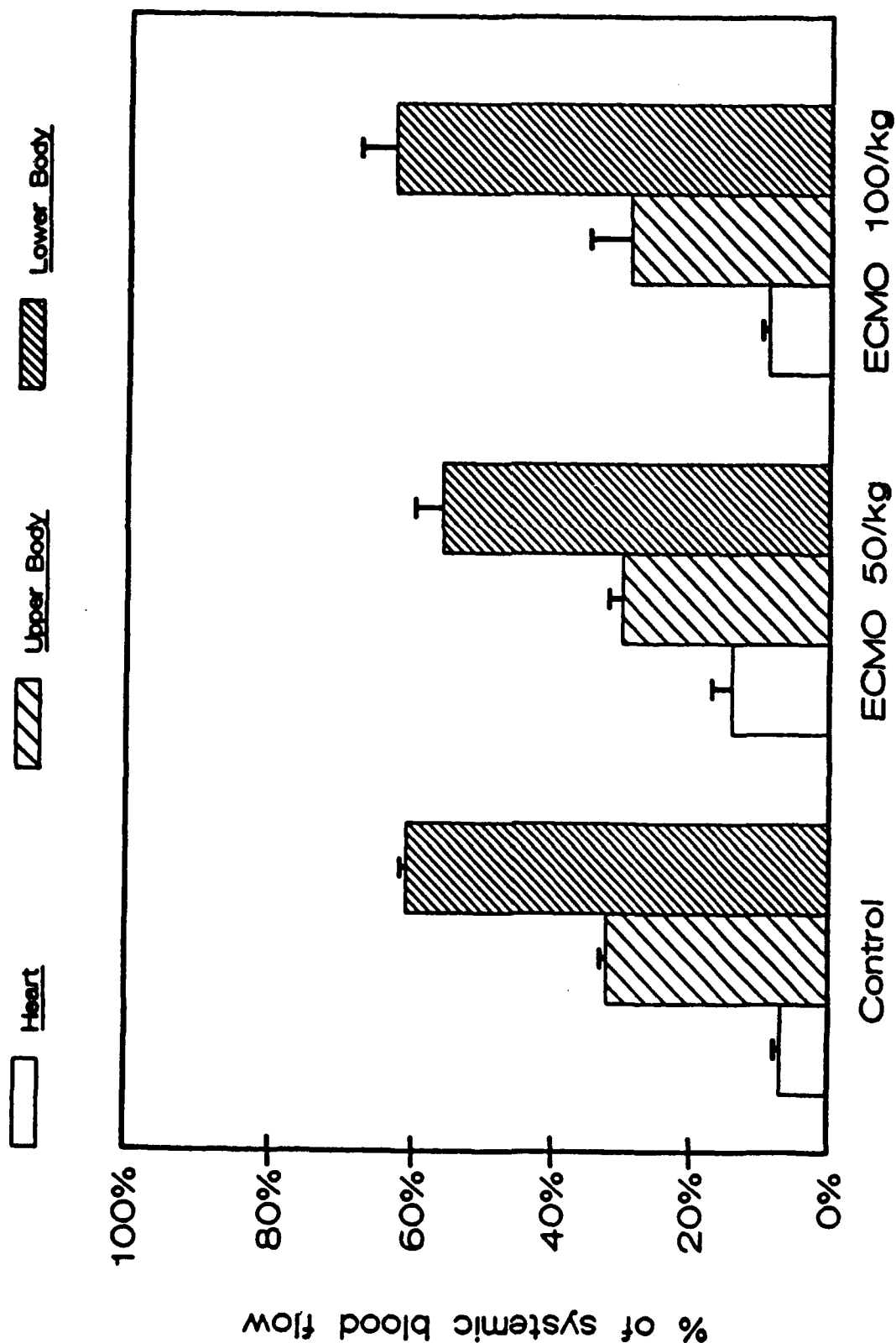


Figure 1. Partitioning of total systemic blood flow to heart, upper body, and lower body for control baseline, ECMO 50 mL/min/kg, and ECMO 100 mL/min/kg flow rates.

% TOTAL SYSTEMIC FLOW: UPPER BODY

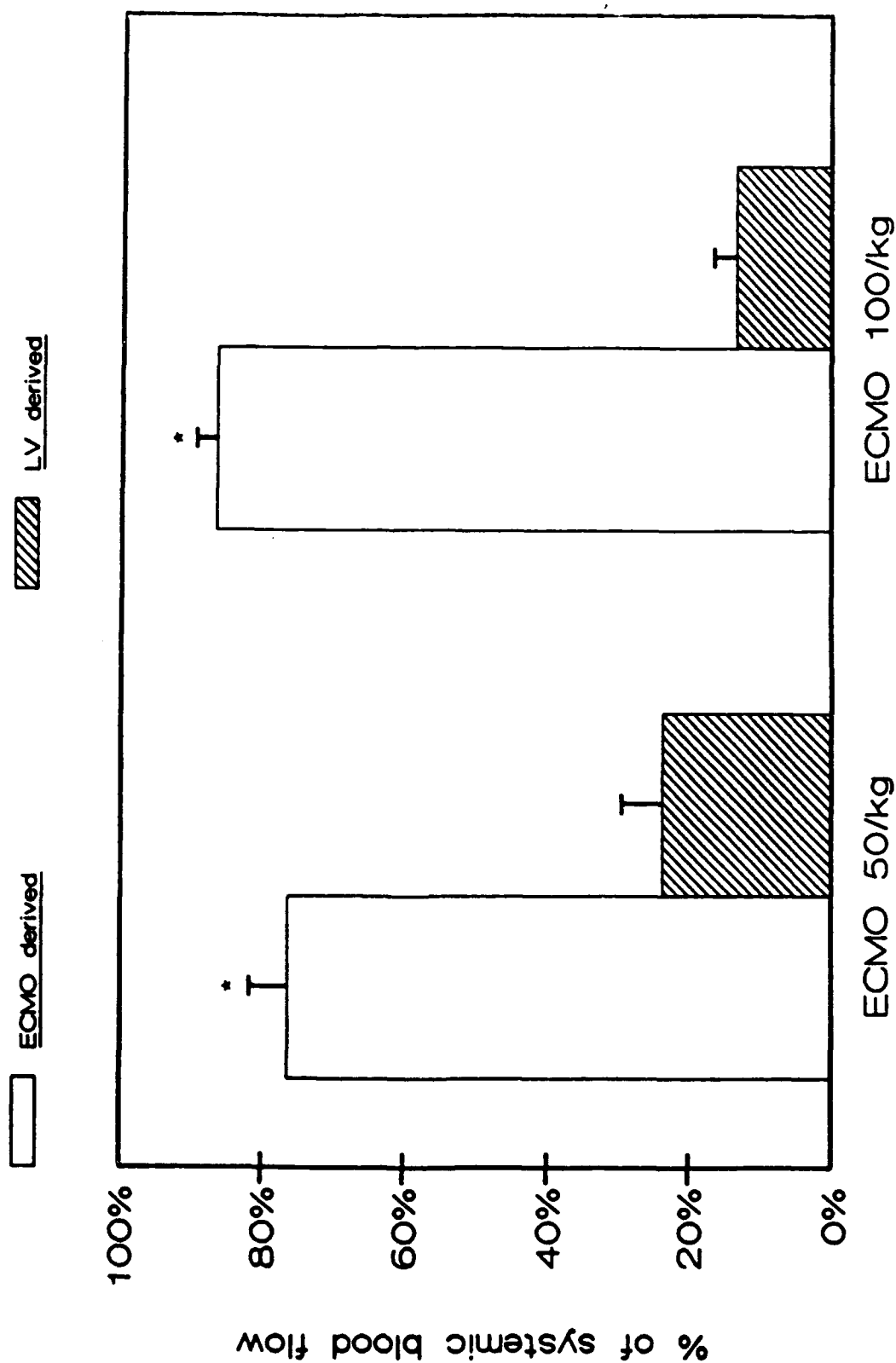


Figure 2a. Percentage of total flow to each compartment derived from ECMO arterial cannula vs. left ventricle.

* = $p < .001$

% TOTAL SYSTEMIC FLOW: LOWER BODY

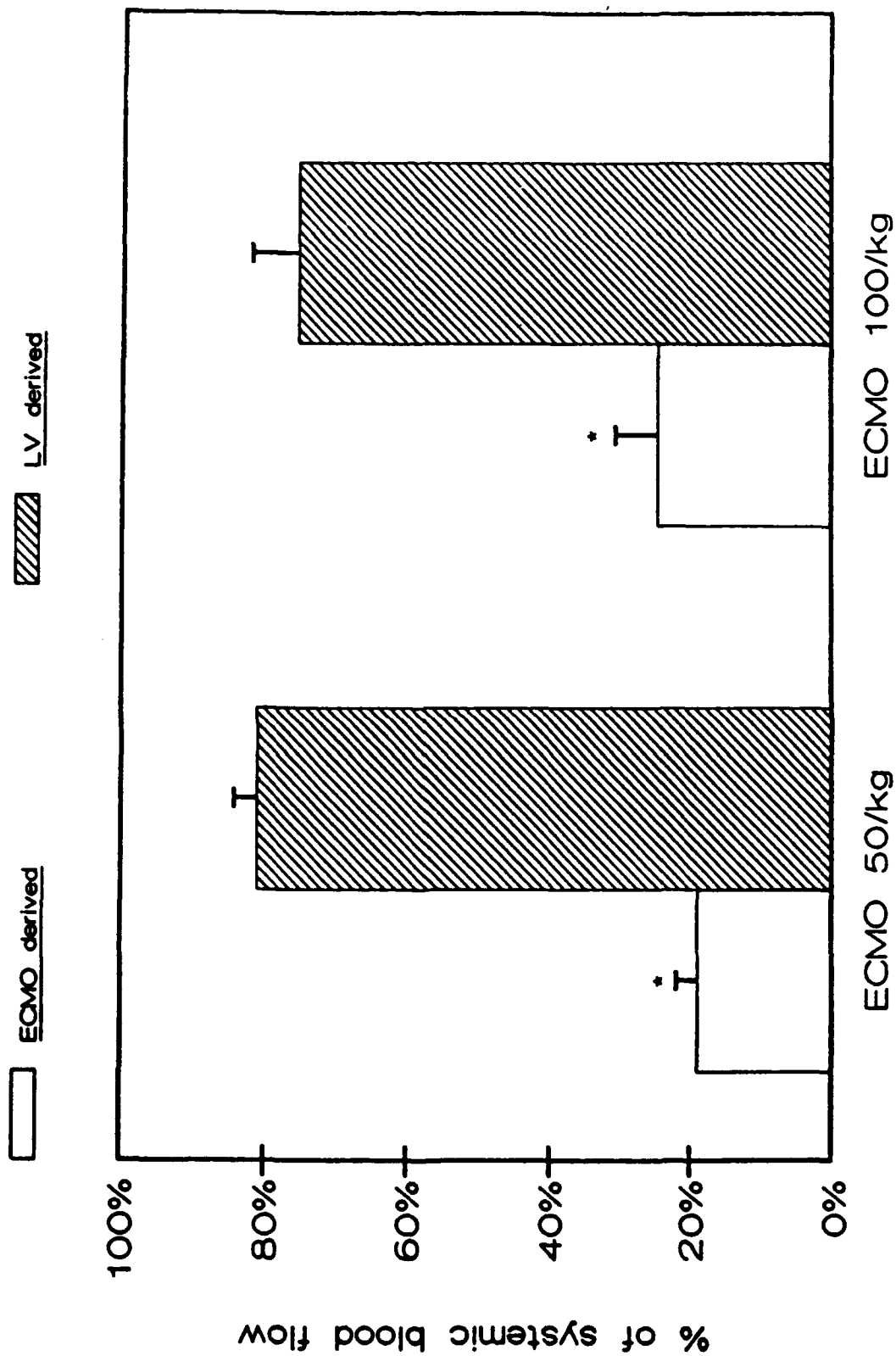


Figure 2b. Percentage of total flow to each compartment derived from ECMO arterial cannula vs. left ventricle.

* = $p < .001$

% TOTAL SYSTEMIC FLOW: HEART

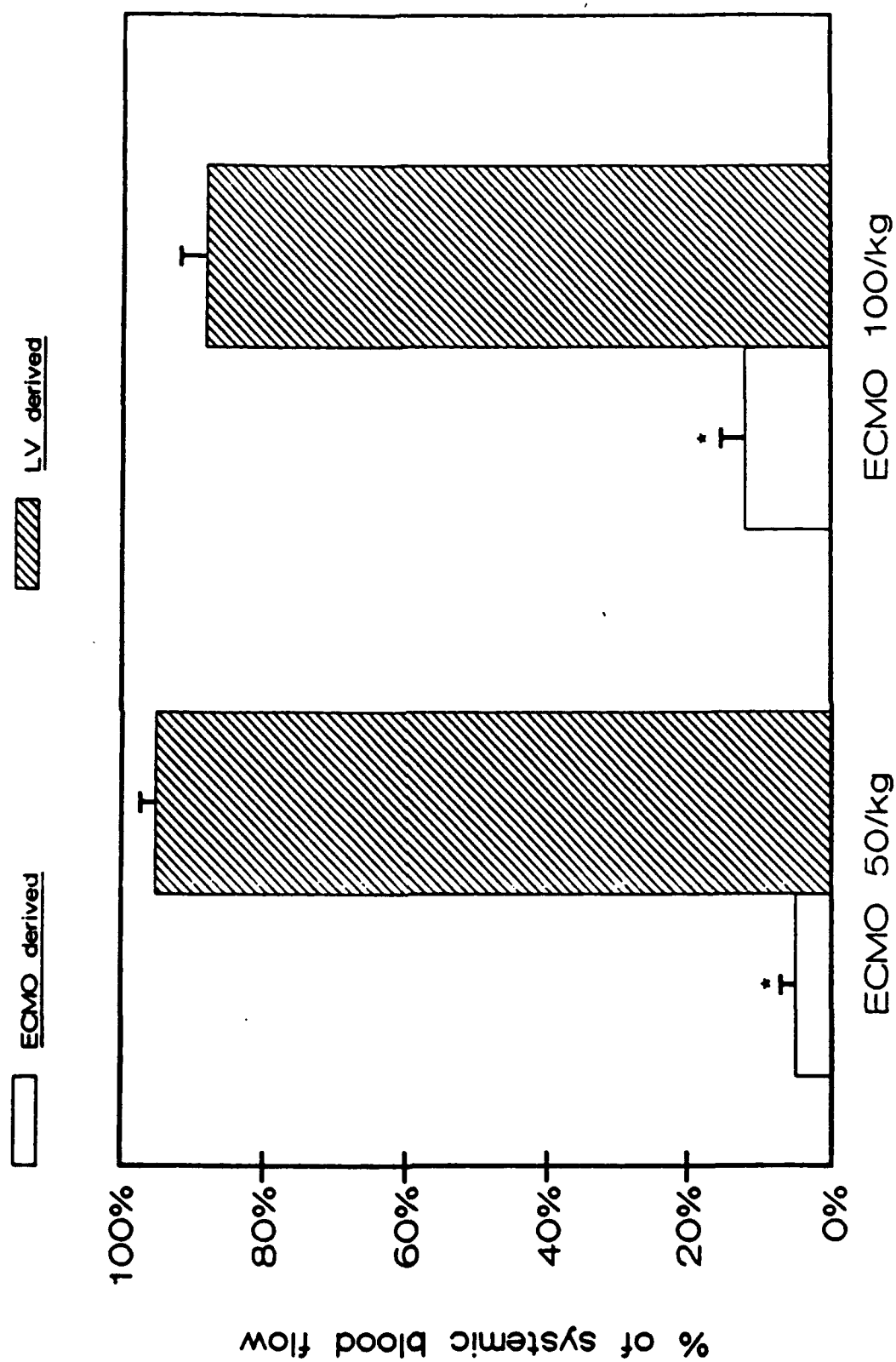


Figure 2c. Percentage of total flow to each compartment derived from ECMO arterial cannula vs. left ventricle.

* = $p < .001$

CORONARY ARTERIAL BLOOD FLOW

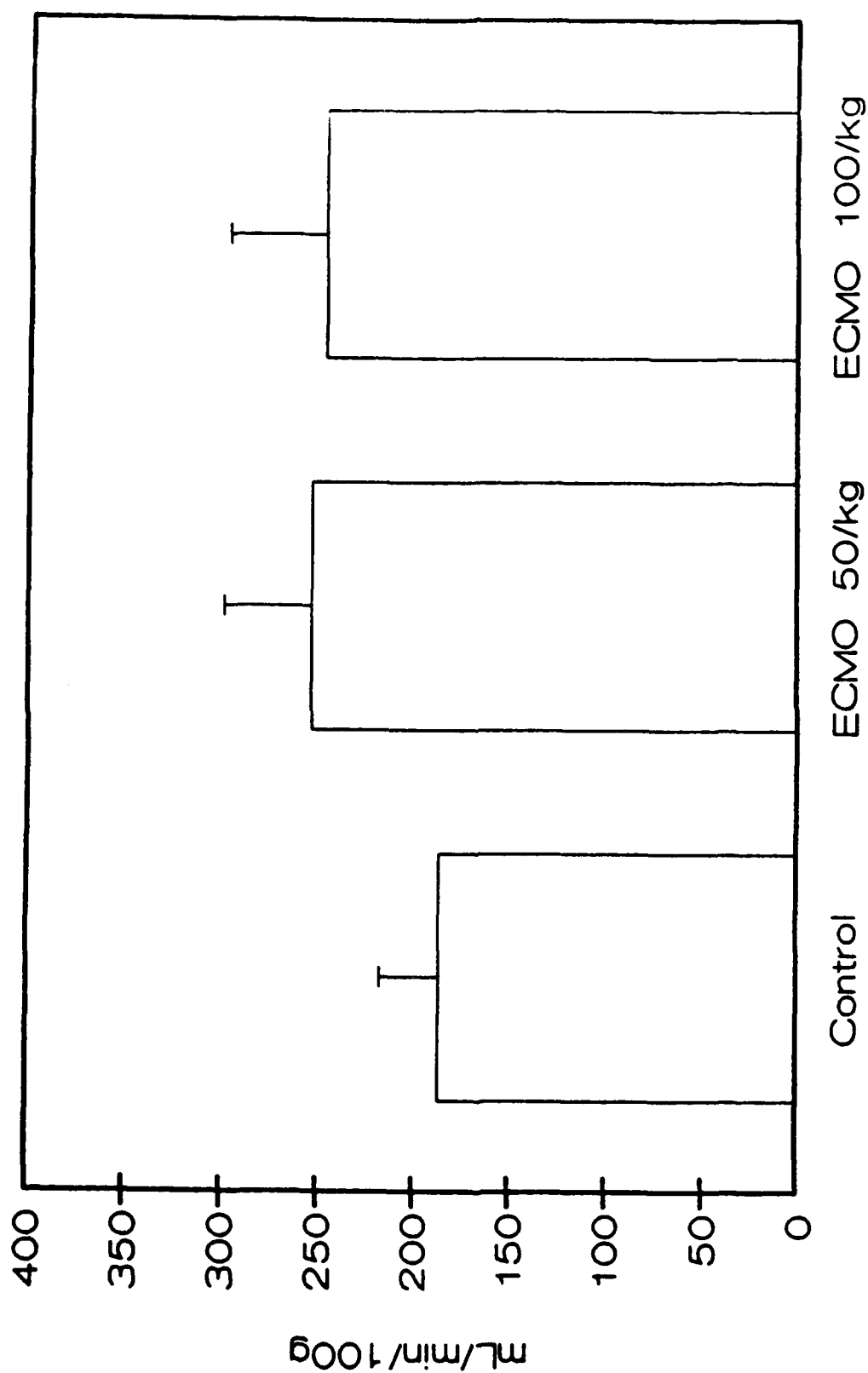


Figure 3. Coronary arterial blood flow (mL/min/100g) for control, ECMO 50 mL/min/kg, and ECMO 100 mL/min/kg flow rates.

Table. Physiologic variables at each microsphere injection timepoint.

	Control	ECMO 50 mL/min/kg	ECMO 100 mL/min/kg	ANOVA p value
pH	*7.35±.02	7.29±.14	7.28±.05	<0.01
PaCO ₂ (mm Hg)	38±2	35±2	35±2	0.49
PaO ₂ (mm Hg)	**128±9	357±59	425±36	<0.01
O ₂ content (uM)	6.7±.3	6.2±.2	6.0±.2	0.14
Heart rate	241±20	212±14	201±13	0.19
MABP (mm Hg)	86±5	71±3	80±10	0.31

* = $p < .05$ vs. 50/100 mL/min/kg.

** = $p < .001$ vs 50/100 mL/min/kg

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APPENDIX

There are two independent sources of systemic blood flow (Q_{es}) during ECMO. These sources are the subject's own left ventricular output (Q_{lvo}) and the additional contribution from the ECMO arterial cannula (Q_{ecmo}). In the three partition model, we assume that Q_{es} supplies three compartments via three separate routes. These are: 1) the heart via coronary arteries (cor); 2) the patent branches of the brachiocephalic trunk, which we will label together as the upper body (ub); and 3) the branches of the aorta distal to the brachiocephalic trunk which is, predominantly, descending aortic blood flow to the lower body (lb). These three routes represent the three flow (Q) compartments of the model.

$$\text{Equation: } Q_{es} = Q_{cor} + Q_{ub} + Q_{lb}$$

Each component of systemic blood flow (Q_{cor} , Q_{ub} , Q_{lb}) must be composed of some fraction of each inflow source (Q_{lvo} , Q_{ecmo}). These fractions are the partition coefficients.

$$\text{Equations: } Q_{cor} = a_1 * Q_{lvo} + b_1 * Q_{ecmo}$$

$$Q_{ub} = a_2 * Q_{lvo} + b_2 * Q_{ecmo}$$

$$Q_{lb} = a_3 * Q_{lvo} + b_3 * Q_{ecmo}$$

In these equations a and b are the partition coefficients,

representing that fraction of each inflow source contributing to the total flow of each partition compartment. Of necessity, $a_1 + a_2 + a_3 = 1 = b_1 + b_2 + b_3$, since flow sources must be conserved. For measurement purposes, flow is sampled at known rates from two of the compartments, that is, there are two arterial reference samples drawn during each measurement on ECMO. One is a branch of the left carotid artery (**ub-ref**) (representing brachiocephalic trunk distribution; upper body), and the other is an abdominal aortic reference sample (**lb-ref**) (representing descending aortic flow; lower body). These reference flows must be some fraction of the total flow to their respective compartments. These fraction constants are labeled as C_{ub} and C_{lb} . The flows Q_{ub-ref} and Q_{lb-ref} are the withdrawal rates of the two syringe pumps in mL/min. These values are known and are shown in bold type in the equations below.

$$\begin{aligned} \text{Equations: } Q_{ub-ref} &= C_{ub} * Q_{ub} = C_{ub} * (a_2 * Q_{lvo} + b_2 * Q_{ecmo}) \\ Q_{lb-ref} &= C_{lb} * Q_{lb} = C_{lb} * (a_3 * Q_{lvo} + b_3 * Q_{ecmo}) \end{aligned}$$

During ECMO, two aliquots of microspheres labeled with different isotopes are simultaneously injected, one into the left ventricle and the other into the arterial limb of the ECMO circuit. The total number of microspheres of isotope #1 (left ventricle) will be labeled 1N , and for isotope #2 (ECMO circuit), 2N . These values are known following necropsy by summing the counts for each isotope from all tissues.

Also known following the experiment are the number of microspheres delivered to the heart for each isotope ($^1N_{hrt}$, $^2N_{hrt}$), and the number which appear in each of the arterial reference samples: ($^1N_{ub-ref}$, $^2N_{ub-ref}$) and ($^1N_{lb-ref}$, $^2N_{lb-ref}$). From these numbers the count ratios, R, are calculated.

$$\begin{aligned} \text{Equations:} \quad & ^1R_{hrt} = ^1N_{hrt}/^1N; & ^2R_{hrt} &= ^2N_{hrt}/^2N \\ & ^1R_{ub-ref} = ^1N_{ub-ref}/^1N; & ^2R_{ub-ref} &= ^2N_{ub-ref}/^2N \\ & ^1R_{lb-ref} = ^1N_{lb-ref}/^1N; & ^2R_{lb-ref} &= ^2N_{lb-ref}/^2N \end{aligned}$$

Since microsphere distribution parallels flow distribution, the fraction of microspheres in each end organ or arterial reference sample must be equal to the fraction of flow reaching that site. Thus a_1 , b_1 and R are related.

$$\begin{aligned} \text{Equations:} \quad & ^1R_{hrt} = a_1; & ^2R_{hrt} &= b_1 \\ & ^1R_{ub-ref} = a_2 * C_{ub}; & ^2R_{ub-ref} &= b_2 * C_{ub} \\ & ^1R_{lb-ref} = a_3 * C_{lb}; & ^2R_{lb-ref} &= b_3 * C_{lb} \end{aligned}$$

The remainder of the model involves solving mathematically for the fraction constants and the flows. To help simplify this process, the ratio constants, K, are calculated.

$$\begin{aligned} \text{Equations:} \quad & K_{ub-ref} = (a_2/b_2) = (^1R_{ub-ref}/^2R_{ub-ref}) \\ & K_{lb-ref} = (a_3/b_3) = (^1R_{lb-ref}/^2R_{lb-ref}) \end{aligned}$$

Derivation:

$$a_1 + a_2 + a_3 = 1$$

$$a_2 + a_3 = (1 - a_1)$$

$$(b_2 * K_{ub-ref}) + (b_3 * K_{ub-ref}) = (1 - {}^1R_{rrt})$$

$$(1 - b_1 - b_3) * K_{ub-ref} + (b_3 * K_{ub-ref}) = (1 - {}^1R_{rrt})$$

$$(1 - b_1) * K_{ub-ref} + b_3 * (K_{ub-ref} - K_{ub-ref}) = (1 - {}^1R_{rrt})$$

$$b_3 * (K_{ub-ref} - K_{ub-ref}) = (1 - {}^1R_{rrt}) - (1 - b_1) * K_{ub-ref}$$

$$b_3 = [(1 - {}^1R_{rrt}) - (1 - {}^2R_{rrt}) * K_{ub-ref}] / (K_{ub-ref} - K_{ub-ref})$$

$$b_2 = (1 - {}^2R_{rrt} - b_3)$$

$$b_1 = {}^2R_{rrt}$$

$$a_3 = b_3 * K_{ub-ref}$$

$$a_2 = b_2 * K_{ub-ref}$$

$$a_1 = {}^1R_{rrt}$$

$$C_{ub} = {}^1R_{ub-ref} / a_2$$

$$C_{ib} = {}^1R_{ib-ref} / a_3$$

$$Q_{ub} = Q_{ub-ref} / C_{ub}$$

$$Q_{ib} = Q_{ib-ref} / C_{ib}$$

$$Q_{ecmo} * (a_3 * b_2 - a_2 * b_3) = (a_3 * Q_{ub} - a_2 * Q_{ib})$$

$$Q_{ecmo} = (a_3 * Q_{ub} - a_2 * Q_{ib}) / (a_3 * b_2 - a_2 * b_3)$$

$$Q_{ivo} = (Q_{ib} - b_3 * Q_{ecmo}) / a_3$$

$$Q_{es} = Q_{ivo} + Q_{ecmo}$$

$$Q_{cor} = Q_{es} - Q_{ub} - Q_{ib}$$

ADDENDUM

The following abstracts were presented:

1. Distribution of systemic blood flow during partial cardiopulmonary bypass in the lamb.
Presented at the 7th annual ECMO symposium; Breckenridge, CO, Feb. 1991.
2. The effect of extracorporeal membrane oxygenation on coronary perfusion and regional blood flow distribution.
Presented at the Society for Pediatric Research; New Orleans, Louisiana, May, 1991.

This contract support was used for the purchase of equipment and supplies; no personnel received pay from these funds.